REMARKS

In the Claims

Claims 29, 61, 63, 65, and 75-79 were considered in the Office Action of July 9, 2010. Claims 34-60, 62, and 67-74 stand withdrawn from consideration. Claims 29, 61, 63, 65, and 75-79 stand rejected.

Applicants hereby amend claims 29 and 61 to improve clarity. Claim 29 has also been amended to correct typographical errors (i.e., to replace "μM" with "μm"). Claim 65 has been amended to provide for proper antecedent basis. Claim 75 has been amended to improve clarity. New claims 80-89 have been added. The amendments to claims 29 and 61 are supported by the originally filed claims and specification (e.g., page 2, line 5; page 7, line 10; page 8, lines 18-24; page 21, line 11; page 11, line 25; page 22, line 11; page 5, lines 14-16; page 8, lines 6 and 20-21; page 10, lines 26-30; page 11, lines 12-16 and 25; and page 12, lines 20-23). Support for the amendments to claim 75 can be found, for example, in the originally filed specification at page 4, lines 15-18. Support for new claims 80 and 82 can be found, for example, in the originally filed specification at page 11, lines 12-16, page 12, lines 23-25; and page 22, lines 10-13. Support for new claims 81 and 83 can be found, for example, in the originally filed specification at page 11, lines 1-6. Support for new claims 84-89 can be found, for example, in the originally filed specification at pages 9-11. No new matter is introduced by these amendments.

Applicants have amended certain claims solely to expedite prosecution of the application. In making these amendments, Applicants are not acquiescing to the pending rejections and are not abandoning or surrendering any of the subject matter in previous versions or listings of the claims or in the application. Accordingly, Applicants reserve the right to pursue claims of similar, narrower, or broader scope in the future.

In view of the amendments to the claims and the following remarks, Applicants respectfully request reconsideration and withdrawal of all grounds of rejection.

Rejection Under 35 U.S.C. § 102(b)

Claims 29, 61, 63, 65 and 75-79 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by PCT Publication No. WO 97/23602 by Baur et al. ("Baur"). Applicants respectfully traverse this rejection below.

Baur reports methods and composition for producing immortalized keratinocytes and melanocytes. More specifically, Baur reports the use of serum-free medium for isolating, producing and maintaining immortalized keratinocytes and/or melanoctyes.

Applicants' invention, as claimed, is a cell suspension comprising viable cells harvested from within the dermal-epidermal junction of a split- or full-thickness skin tissue sample. As clearly recited in independent claims 29 and 61, the cell suspension of Applicants' invention comprises a cell suspension having the following features:

(1) viable **keratinocyte basal cells** harvested from the epidermal surface at the dermal-epidermal junction of the skin tissue sample;

(2) viable **melanocytes** harvested from the epidermal surface at the dermal-epidermal junction of the skin tissue sample;

(3) viable **fibroblasts** harvested from the dermal surface at the dermal-epidermal junction of the skin tissue sample;

(4) the keratinocyte basal cells, melanocytes, and fibroblasts referenced in nos. (1), (2) and (3) are **autologous to the patient** from which the sample was obtained (i.e., all of the cell types are from the same single origin);

(5) ratios of the cell types referenced in nos. (1), (2) and (3) (i.e., the ratios being keratinocyte basal cells to melanocytes, keratinocyte basal cells to fibroblasts, and melanocytes to fibroblasts) **that are comparable to the ratios of such cell types in situ** within the dermal-epidermal junction from which the cell were harvested;

(6) a nutrient solution that is **free of serum xenogenic the patient** referenced in no. (4) (i.e., the nutrient solution is free of serum that is of a different origin than the cells); and

(7) the **absence of cellular congregates greater than 200 μm**.

While neither the skin tissue sample nor the donor of the skin tissue sample (i.e., the patient) are themselves limitations within Applicants' claims, the skin tissue sample and the patient are used as points of reference in defining certain features of the invention, thereby defining certain

structural aspects and relationships between the features. For example, Applicants' cell suspension requires keratinocyte basal cells, melanocytes, and fibroblasts that have been harvested from the same, single origin, and present in ratios that are defined using the in situ ratios of such cells as a point of reference.

In the final Office action of July 9, 2010, the Examiner rejected Applicants' claims as being anticipated by Baur, asserting that "the only material requirement limiting the compositions in claim 29 and 61 is that they contain keratinocyte basal cells, melanocytes, and fibroblasts in a suspension lacking cellular congregates (e.g., a single-cell suspension) and further lacking xenogenic serum. … Baur's composition contains all of the positively recited elements of applicants' claims and lacks the necessarily excluded elements." See Office action at page 3. In making this rejection, the Examiner appears to ignore Applicants' recited limitation that the cell suspension is free of cellular congregates greater than 200μm, and dismisses Applicants' recited limitation that the cell suspension comprises a cell population of keratinocyte basal cells, fibroblasts and melanocytes that is comparable to the population of such cells found in the skin tissue sample from which they were harvested.

Anticipation under 35 U.S.C. § 102 requires that each and every element of the claims must be found, either expressly or inherently described, in a single prior art reference. See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F. 2d 628, 631 (Fed. Cir. 1987). It is not enough that each element is individually found in the prior art reference, the reference must show the identical invention in as complete detail as is contained in the claim. See *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236 (Fed. Cir. 1989). Indeed, the elements must be arranged as required by the claim. See *In re Bond*, 910 F. 2d 831 (Fed. Cir. 1990). That requires that the anticipatory reference show "all of the limitations of the claims arranged or combined in the same way as recited in the claims, not merely in a particular order." *Net MoneyIN, Inc. v. Verisign, Inc.* 545 F.3d 1359 (Fed. Cir. 2008) Moreover, according to M.P.E.P § 2131.03, "anticipation under § 102 can be found only when the reference discloses exactly what is claimed ….". (Emphasis added.) See *Titanium Metals Corp. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985). Furthermore, "[a] single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.,* 311 F.3d 1116 (Fed. Cir. 2002). (Emphasis added).

Additionally, "[t]he disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." M.P.E.P § 2121.01, citing *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research,* 346 F.3d 1051, 1054 (Fed. Cir. 2003). (Emphasis added.) To be enabling, the reference must show that the public was in possession of the claimed invention at the time the invention was made. Such possession is only effected if "one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention." See *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).

Applicants submit that Baur does not anticipate Applicant's claimed invention because the disclosure of Baur is ambiguous, inconsistent, and certainly insufficient to establish that Applicants' clamed invention existed in the prior art. Furthermore, even taken as a whole, the confusing disclosure of Baur completely fails to enable one skilled in the art to make and use the Applicants' claimed invention. As Baur in no way meets even the minimum requirements for anticipatory reference, Applicants' submit that the rejections under § 102 in view of Baur cannot stand.

A. BAUR FAILS TO PROVIDE SUFFICIENT PRECISION AND DETAIL TO ESTABLISH THAT THE CLAIMED SUBJECT MATTER WAS IN THE PRIOR ART

An anticipatory reference must unambiguously and unequivocally disclose each and every limitation of the claim, as arranged in the claim, in sufficient precision and detail to establish that the claimed invention was in the prior art. See *Application of Sheppard*, 339 F.2d 238 (C.C. P.A. 1964); *Application of Hughes*, 345 F.2d 184 (C.C.P.A. 1965). Applicants submit that Baur fails to clearly disclose (1) a cell suspension comprising keratinoctye basal cells, melanocytes, and fibroblasts; (2) ratios of cell types comparable to those found in situ; and (3) the absence of cellular congregates greater than 200 μM.

1. *Cell Suspension Comprising Keratinocyte Basal Cells, Melanocytes, and Fibroblasts*

At the crux of this rejection is the Examiner's allegation that "Baur teaches a cell suspension comprising melanocytes, keratinocytes, and fibroblasts in a serum free medium."

See Office action at page 3. The Examiner cites to two passages in support, but contrary to the Examiner's allegation, these passages completely fail to unambiguously and unequivocally teach a cell suspension comprising melanocytes, keratinocytes, and fibroblasts. In fact, the disclosure of Baur is so imprecise and lacking in detail that it simply cannot be relied upon as an anticipatory reference.

The two passages in Baur to which the Examiner cites are found at Example 3, page 23, lines 19-21 and at page 15, lines 19-21. In fact, Baur makes three references, and *only* three references, to a cell suspension, all in exactly the same context. In each instance, Baur indicates that the cell suspension was discussed or described elsewhere; and in two of the instances, Baur references Example 1. Applicants note that the three references below are the *only* passages in Baur that refer to fibroblasts in the same context as the isolated keratinocytes and melanocytes. In fact, there is no further reference to fibroblasts in connection with the cell suspension in any of those passages. In all three instances, the only cells referred to thereafter are keratinocytes and/or melanocytes.

At page 15, lines 19-26:

> "**As discussed**, a cell suspension produced from a single skin sample which contains dissociated melanocytes, keratinocytes and fibroblasts will preferably **be cultured in the subject NR-3 medium**. This will be effected by **seeding such cells onto culture dishes** which are continuously coated with a composition which facilitates their attachment…This coating or **'cocktail' coating has been previously described for bronchial cells (Lechner et al., J. Tiss, Cult. Meth. 9:43-48 (1985)…"**
>
> (**Note:** No further reference is made to fibroblasts in the context of the quoted discussion. Bolded emphasis added.)

At Example 3, page 23, lines 19-24:

> "1) Immortalization of **Keratinocytes**: a cell suspension produced from skin samples **described in example 1**, which contains dissociated melanocytes, keratinocytes and fibroblasts, **are cultured in the subject NR-3 medium.** This is effected by **seeding such cells onto culture dishes** which are continuously coated with the **'cocktail' coating previously described for bronchial cells (Lechner et al., J. Tiss, Cult. Meth. 9:43-48 (1985)…"**
>
> (**Note:** No further reference is made to fibroblasts in the context of the quoted discussion. Bolded emphasis added.)

At Example 4, page 30, lines 31-34:

> "1) Immortalization of **melanocytes**: a cell suspension produced from skin sample DK0-NR **described in example 1**, which contains dissociated melanocytes, keratinocytes and fibroblasts, **are cultured in the subject NR-3 medium.** This is effected by **seeding such cells onto culture dishes** which are continuously coated with the **'cocktail' coating previously described for bronchial cells (Lechner et al., J. Tiss, Cult. Meth. 9:43-48 (1985)** …"
>
> (**Note:** No further reference is made to fibroblasts in the context of the quoted discussion. Bolded emphasis added.)

Each and every one of the above references to a cell suspension is made the context of a specific step of a method disclosed by Baur at pages 7-9 for preparing immortalized keratinocytes and/or melanocytes. That step is step (iii), which describes obtaining keratinocytes and/or melanocytes from a skin tissue sample that has been prepared for *in vitro* culturing per step (ii), and seeding them onto culture plates. More specifically, the method comprises steps (i)- (viii) which recite the following:

> (i) obtaining a human skin tissue sample;
>
> (ii) preparing said skin sample for culturing *in vitro*;
>
> (iii) obtaining **keratinocytes and/or melanocytes** from said prepared skin sample and seeding said **keratinocytes and/or melanocytes** into a serum-free growth medium, preferably either the NR-3 medium or NR-4 (for melanocytes) (described infra) onto culture plates provided with a coating which facilitates cell attachment and cell growth, **said coating comprising fibronectin, type 1 collagen and BSA.**
>
> (iv) changing the medium as necessary o optimize confluent growth of the cultured cells while continuously maintaining the coating on the cultured plates;
>
> (v) transferring the **keratinocytes or melanocytes** into an [sic] selection medium…
>
> (vi) infecting the **keratinocytes or melanocytes** with a retroviral construct…
>
> (vii) transferring the resultant immortalized **keratinocytes or melanocytes** to a proliferation medium…
>
> (viii) transferring the resultant immortalized **keratinocytes or melanocytes** to a differentiation medium…

(Baur, page 7, lines 16 through page 8, line 9; emphasis added.)

Baur further describes step (iii), in the context of step (ii), at page 8, line 16 through page 9, line 15 as follows:

> The skin sample will then be prepared in step (ii) such that it is suitable for culturing in vitro. This will preferably be effected by initially washing the skin sample … After washing, the skin sample will then preferably be **shaved, e.g. with a dermatome, and then excised into small pieces**.
>
> The resultant skin sections are then preferably **separated into dermis and epidermis**. This may be effected by physical and/or enzymatic means. For example, this may be effected by trypsinization, e.g. by floating skin sheets in a trypsin solution (e.g. about 0.5%) containing EDTA (e.g. about 0.1%) **for a sufficient time to effect cell separation**[1], e.g. about 30-60 minutes at 37 °C or overnight at 4°C.
>
> The **dermis is separated (to isolate the fibroblasts, see EXAMPLE 2 and the epidermis is then placed in a suspension medium**. Preferably the **suspension medium** will contain soybean trypsin inhibitor solution (SBTI) and will be contacted with the cells for a sufficient time, typically about 5 minutes, in order to inactivate the trypsin and provide for **cell release** Tissue culture medium will then be added, preferably serum-free NR-2 medium (described *infra*) and a filter (e.g. 100 mm filter) to obtain the desired cells, i.e. **keratinocytes and/or melanocytes**.
>
> **The resultant primary keratinocyte/melanocyte culture obtained in step (ii)** is then seeded into serum-free medium, preferably NR-3 medium (described in detail infra), at a suitable cell concentration, preferably about 1.2×10^4 cells/cm^2, onto precoated culture plates. However, this cell concentration may be varied within wide limits. The culture plates are preferably continuously coated with a composition which has been surprisingly found to enhance both the attachment and growth of **keratinocytes and melanocytes**, specifically a solution of **fibronectin, BSA and collagen type 1. This cell coating composition has previously been described for use with bronchial cells. (Lechner et al, J. Tissue Cult. Meth. 9:43-48 (1985)),** which reference is incorporated by reference herein.

(Emphasis added.)

Importantly, the *only* references to a suspension medium in Baur are shown above with clearly describe that keratinocytes and melanocytes, *and only keratinocytes and melanoocytes*, are isolated a suspension medium.. As quoted above, Baur expressly discloses in step (ii) separating the dermal layer from the epidermal layer, placing the epidermis in a suspension medium, and isolating melanocytes and/or keratinocytes from the epidermis in the suspension medium, thereby producing a cell suspension comprising melanocytes and/or keratinocytes isolated from a

[1] Taken with the paragraph immediately following, "cell separation" cannot be interpreted as release of individual cells as the following paragraph refers to separation of dermis and epidermis and cell release from the epidermis.

single skin sample. Baur refers the reader to Example 2 for a description of isolating fibroblasts from the dermal layer.

At Example 1 (rather than Example 2), Baur describes isolating fibroblasts. The totality of this Example is as follows:

> **EXAMPLE 1:** Characterization of Established Skin Cells
>
> Table 1 lists all skin samples which were processed for viral infection. The isolated keratinocytes which show the best cell growth were used for immortalization.
>
> **[TABLE 1 Skin Samples Used for Cell Isolation in NR- Medium]**
>
> Human fibroblasts were isolated from the skin samples FK0-NR, GK0-NR, DK0-NR. **After the separation of the dermal and epidermal compartment**, the **dermis** was **cut into small pieces 0.2 x 0.2 mm** and fixed on a 6cm culture plate with serum. Dulbecco's minimal essential medium (DMEM, 10%FCS) was added after 2-4 hours. This **explant culture** was then incubated until **fibroblast outgrowth** was visible. Confluent fibroblast cultures were split and expanded for frozen stocks.

(Unabridged, emphasis added.)

Example 1 clearly provides that after the epidermis and dermis are separated (as provided in step (ii)), the dermis is cut into pieces, and plated as an **explant** culture until fibroblast outgrowth from the explant culture was observed. In the preparation of the primary culture according Baur, the fibroblasts **are never** dissociated. In fact, there is nothing in Example 1, or anywhere in the description of the method, that could reasonably be interpreted as providing a cell suspension comprising dissociated fibroblasts, let alone a cell suspension comprising melanocytes, keratinocytes, **and fibroblasts**.

Each time Baur refers to a cell suspension, it is in the context of steps (ii)-(iii) of the method that is described at pages 7-9 and/or in Example 1. The method described by Baur fails to produce a cell suspension that comprises dissociated keratinocytes, melanocytes, and fibroblasts. Taken in view of the full disclosure of Baur and placed in the context of Example 1 and step (iii) of the method of Baur, the reference to a "cell suspension produced from a single skin sample [described in example 1 which contains dissociated melanocytes, keratinocytes and fibroblasts" could only be understood to refer to the cell suspension of step (ii), which comprises the isolated melanocytes and/or keratinocytes. The reference could be understood to mean that these suspensions were produced from the skin samples identified in Example 1. At step (iii) each

skin sample now consists of, or contains, isolated, or "dissociated"[2], melanocytes and/or keratinocytes from the epidermal layer; and separately isolated fibroblasts from the dermal layer. Though perhaps inartful, that is the only interpretation of those passages that makes sense in the context of the disclosure of Baur. As such, Applicants respectfully submit that Baur fails to adequately disclose any cell suspension comprising keratinocyte basal cells, melanocytes, and fibroblasts as required by Applicants' claimed invention.

2. *Ratios of Cell Types Comparable to Those Found In Situ*

As an initial matter, the Examiner must consider Applicants' claimed invention *as a whole*. That means that each and every element of Applicants' invention, as recited by the claims, must be given due consideration. Applicants' respectfully submit that, in rejecting Applicants claims based on the disclosure of Baur, the Examiner has improperly dismissed Applicants' express limitation regarding the "comparable" cell population by refusing to apply the ordinary and customary meaning of the term "comparable", and has ignored the express claim limitation that the cell suspension of Applicants' invention be free of cell congregates greater than 200 μm. Applicants address each of these limitations below.

In the Office action of July 9, 2010, the Examiner dismisses that express feature of Applicants' claimed invention that the cell suspension comprise a cell population of keratinocyte basal cells, fibroblasts and melanocytes that is comparable to the population of such cells found in the skin tissue sample from which they were harvested. The Examiner asserts that "Applicants allege that the term 'comparable' should be interpreted as 'similar.'...However, the term 'comparable' is not explicitly provided with such a limiting definition, and in any case, the degree of 'similarity' is not limited in the claims or specification. The constituents in the suspension of Baur are necessarily comparable to some degree with the tissue that gave rise to that suspension." Office action at page 6.

According to M.P.E.P. § 2111, during patent examination, the pending claims must be given their broadest reasonable interpretation but that interpretation must be consistent with the specification, and consistent with that those skilled in the art would reach. See *In re Cortright*,

[2] Applicants note that the references to a cell suspension is the only places where 'dissociated' is used.

165 F.3d 1353, 1359, 49 USPQd 1464, 1468 (Fed. Cir. 1999). The Patent Office must apply the broadest reasonable meaning of the words "in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that be afforded by the written description contained in applicant's specification." M.P.E.P. § 2111, citing *In Re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). (Emphasis added.) "It is the use of the words in the context of the written description and customarily by those skilled in the relevant art that accurately reflects both the 'ordinary' and the 'customary' meaning of the terms in the claims." M.P.E.P. § 1101.01, citing *Ferguson Beauregard/Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed Cir 2003).

As amended, Applicants' claims recite a cell suspension comprising keratinocyte basal cells, melanocytes and fibroblasts, wherein the ratios of each cell type to each other cell type in the cell suspension is comparable to the ratios of such cell types in situ within the dermal-epidermal junction from which the cell types were harvested. As used in Applicants' claims, "comparable" means similar. See April 29, 2010 Amendment and Response, page 12. That meaning is wholly consistent with the disclosure Applicants' specification in which Applicants describe harvesting cells from a dermal-epidermal junction and directly preparing a cell suspension with the harvested cells. Nowhere in Applicants' specification is there any teaching or suggestion that any methods for enrichment or selection for any particular cell type is used in the making of Applicants' claimed invention. Following the methods of Applicants' specification, one would produce a cell suspension having cell types in ratios to each other that are similar or substantially equivalent to those ratios of such cell types as found in situ in the dermal-epidermal junction. Further support for this interpretation is provided at page 12, lines 23-30, and at page 8, lines 18-24, where Applicants teach that the cell suspensions of the invention comprise different cell types in ratios that are comparable to those seen in situ from where the cells were harvested in contrast to the prior art in which selective culture for keratinocytes would result in loss of any other cell types that were co-harvested with the keratinocytes.

In the context of Applicants' disclosure, the ordinary and customary meaning of the term "comparable" is "similar, which is consistent with how those skilled in the art would have used it (and in fact continue to use it). As an example of such use, Applicants refer the Examiner to

DeLuca, M., "Human Epithelial Cells Induce Human Melanocyte Growth In Vitro But Only Skin Keratinocytes Regulate Its Proper Differentiation in the Absence of Dermis", J. Cell. Biol., 107: 1919-1926 (1988) ("DeLuca")[3]. DeLuca examines the ratio of melanocytes to keratinocytes (M/K ratio) in various cultures. At page 1921, left column, and in Figure 2, DeLuca compares the M/K ratio of various strains, reporting that "…in all cell strains the final M/K ratio was **comparable** to the ratio determined in the presence of a feeder layer (Fig. 2, *lower panels*)." Figure 2 of DeLuca shows that the M/K ratios were indeed similar. As another example of such use of the term "comparable", Applicants refer the Examiner to Young, A., "Human Melanocytes and Keratinocytes Exposed to UVB or UVA In Vivo Show Comparable levels of Thymine Dimers, " J. Investigative Dermatology, 111 (6): 936-941 (1998) ("Young")[4]. At page 939, left column, lines 7-19, Young reports that their results "show that melanocytes and adjacent keratinocytes have **comparable** sensitivity to TT [thymine dimers] induction at the UVB and UVA wavebands." (Emphasis added.) At Figure 2, Young shows those results as the TT response data for melanocytes and keratinocytes at the UVB and UVA wavebands. The legend for Figure 2 reports that "[d]ose-response curves for thymine dimers in melanocytes and basal kerotinocytes are **similar** at UVB and UVA wavelengths studied." (Emphasis added.) As used in Applicants' claims, those skilled in the art at the time of the invention would have *only* understood the word "comparable" to mean similar--i.e., that the cell population of Applicants' cell suspension contains a cell population that is similar to the cell population found in situ. As an express limitation of Applicants' claimed invention, the Examiner cannot simply dismiss it by refusing to accord the term "comparable" with its ordinary and customary meaning as one skilled in the art would understand it to mean.

As discussed above, Baur fails to provide a clear disclosure of a cell suspension comprising keratinocyte basal cells, melanocytes and fibroblasts. Because Baur utterly fails to provide any level of detail or precise teachings of such a cell suspension, Baur necessarily fails to disclose a cell suspension in which the ratios of such cell types are comparable to that found in situ.

[3] A copy of this reference is included with the Information Disclosure Statement filed herewith.
[4] A copy of this reference is included with the Information Disclosure Statement filed herewith.

3. *Absence of Cellular Congregates Greater Than 200 μm*

While Applicants disagree with the Examiner's assertion that Baur anticipates a cell suspension comprising fibroblasts, Applicants also respectfully disagree with the particular assertion by the Examiner that Baur discloses a cell suspension that lacks cellular congregates grater than 200 μm. Applicants note that the Examiner has characterized the Applicants' claimed limitation of "free of cellular congregates greater than 200 μm" as "lacking cellular congregates (e.g., a single-cell suspension)". Applicants respectfully request that the Examiner address the limitations as expressly recited in Applicants' claims rather than as characterized in the Examiner's own words.

According to the Examiner, "Baur characterized the cells as 'dissociated' and 'separated,' indicating that the suspension is a single-cell suspension." In support, the Examiner points to page 15, line 20 where it refers to "dissociated melanocytes, keratinocytes, and fibroblasts" (i.e., the language discussed above) and the description at page 8, line 30, where Baur describes "cell separation" in the context of step (ii) in which the skin sample is separated into dermis and epidermis, well before any suspension of keratinocytes and/or melanocytes is made. As noted above, the sole reference Baur makes to "dissociated" cells (or the dissociation of cells, for that matter,) is with respect to the "cell suspension produced from a single skin sample which contains dissociated melanocytes, keratinocytes, and fibroblasts"). Applicants respectfully request that the Examiner provide evidence to support the assertion that "dissociated" cells and "separated" skin layers indicates a single-cell suspension. More to the point, Applicants respectfully request that the Examiner provide evidence to support the assertion that such references indicates a cell suspension which is free of cellular congregates greater that 200 μm, as expressly recited in Applicants' claims. As the Examiner is well aware, cell suspensions may include cellular congregates along with single cells. In fact, the Examiner admitted at page 5 of the Office action that "Baur does not explicitly teach that large cell aggregates are absent from the suspension." In fact Baur fails to provide any disclosure of a cell suspension according to Applicants' claimed invention that is free of cellular congregates greater than 200 μm.

B. THE DISCLOSURE OF BAUR FAILS TO ENABLE ONE SKILLED N THE ART TO MAKE AND USE THE CLAIMED INVENTION

As discussed above, the disclosure of Baur is ambiguous and lacking in precision and detail. It is inconceivable that the grossly insufficient disclosure of Baur could possibly be deemed to enable one skilled in the art to make and use the very cell suspension that Baur fails to describe. In fact, Baur provides absolutely no description whatsoever of how to make or use a cell suspension comprising keratinocyte basal cells, melanocytes and fibroblasts, and necessarily fails to describe the ratios of cell types as recited in Applicants' claims. Baur merely names the subject matter of Applicants' claimed invention--i.e., a "cell suspension". That is wholly insufficient to enable one skilled in the art to make and use the cell suspension of Applicants' clamed invention.

Again, as previously discussed, the method of Baur requires that the skin sample be separated into a dermis and an epidermis. Only the epidermis is placed in a suspension medium and subjected to conditions to provide for cell release and only keratinocytes and/or melanocytes are isolated. It is **only** this cell suspension --i.e., the cell suspension that includes only keratinocytes and/or melanocytes--that is processed through steps (iii) - (viii). Indeed, there is no mention whatsoever of the dermis or fibroblasts thereafter in steps (iii) - (viii). The sole remaining reference to the dermis or the dermal fibroblasts is the single paragraph of Example 1.

Turning again to Example 1, Applicants point out again that Baur explicitly describes isolating fibroblasts from the **separated dermis** by way of **explant culture** -- i.e., the tissue is minced but not subjected to conditions for release of cells, and the minced tissue is culture on a plate until fibroblast outgrowth. Not only does Baur fail to provide an enabling disclosure of a cell suspension from the dermis or comprising fibroblasts, the methods disclosed by Baur are in direct contradiction to that which would be required to enable one skilled in the art to make or use Applicants' claimed invention.

Aside from the ambiguous language cited by the Examiner, the very idea that Baur would disclose a cell suspension comprising dissociated melanocytes, keratinocytes, and fibroblasts defies both logic and conventional wisdom. Baur is narrowly focused on providing immortalized keratinocytes and melanocytes. The only reference to fibroblasts other than Example 1 is as

feeder layer cells (e.g., page 5, line 10) or as potential contaminants (e.g., page 15, lines 13-16). The standard method for isolating keratinocytes and melanocytes from skin samples was just as described by Baur--separating the epidermis and dermis by enzymatic means and subjecting the epidermis to conditions to allow for cell release. (See Macdiarmid, J. "Separation of Epidermal Tissue from Underlying Dermis and Primary Keratinocyte Culture," Methods Mol. Biol. 174: 401-410 (2001) provided as an Attachment to the Declaration submitted on September 9, 2010). Baur further teaches separate handling of the intact dermis to culture fibroblasts for frozen stocks. There is not a single moment in the method of Baur in which a cell suspension exists that comprises dissociated melanocytes, keratinocytes, and fibroblasts.

If the Examiner would have Applicants believe that Baur teaches adding fibroblasts from the frozen stocks to the cell suspensions comprising keratinocytes and/or melanocytes, Applicants submit that one skilled in the art would not be enabled by the disclosure of Baur to do so. As described in Jensen, P. et al., "Cultivation at Low Temperature as a Measure to Prevent Contamination with Fibroblasts in Epithelial Cultures From Human Skin", J. of Investigative Dermatology, 77, 210-212 (1981)[5]; and Drewa, T. et al., "Does the Presence of Unwanted Dermal Fibroblasts Limit the Usefulness of Autologous Epidermal Keratinocyte Grafts?", Transplantation Proceedings, 38: 3088-3091 (2006)[6], even a minimal number of contaminating fibroblast cells can quickly outgrow a culture of epidermal cells. As demonstrated by the foregoing references, it is a problem that was recognized before the disclosure of Baur and is still unresolved. Baur would be inoperable if interpreted to disclose a 'cell suspension comprising dissociated melanocytes, keratinocytes and fibroblast' because the cell cultures made from these cell suspensions would be overgrown with fibroblast proliferation and the cell cultures would be rendered unusable for the methods of Baur.

As such, the disclosure of Baur fails to enable one skilled in the art to make and use Applicants' claimed invention. Applicants further submit that the mere and ambiguous references at page 15, lines 19-21, page 23, lines 19-21, and page 30, lines 30-32, cannot be reasonably or fairly be interpreted in view of Baur, as a whole, as a disclosure of a "cell suspension comprising dissociated melanocytes, keratinocytes and fibroblasts."

[5] A copy of this reference is included with the Information Disclosure Statement filed herewith.
[6] A copy of this reference is included as an attachment (Exhibit A) for the convenience of the Examiner.

Because the disclosure of Baur fails to describe each and every limitation of Applicants' claimed invention, and necessarily fails to enable one skilled in the art to make and use Applicants' claimed invention, Applicants respectfully submit that claims 29, 61, and dependent claims 63, 75-79 are not anticipated by Baur. Accordingly, Applicants request that the rejection of these claims under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejection of Claim 65 Under 35 U.S.C. § 102(b)

Claim 65 was separately rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Baur in view of U.S. Patent No. 6,432,666 to Hart ("Hart"). According to the Examiner, Hart was relied upon as teaching that trypsinized skin suspensions contain Langerhans cells. Claim 65 depends upon claim 61. Claim 61 as amended is patentable over Baur for reasons discussed above. Hart does not remedy the deficiencies of Baur at least because Hart is cited solely as teaching that trypsinized skin suspensions contain Langerhans cells. Accordingly, claim 65 cannot be anticipated by Baur even in view of Hart.

For the reasons provided above, Applicants respectfully submit that claim 65 is not anticipated by Baur. Accordingly, Applicants request that the rejection of these claims under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 29, 61, 63, 65 and 75-79 stand rejected under 35 U.S.C. § 103 as allegedly being obvious over Baur in view of Lucas et al., U.S. Patent No. 5,328,695 ("Lucas") and Hart. Applicants respectfully submit that Baur, even in view of Lucas and Hart, does not render obvious Applicants' invention, as claimed. Specifically, Baur, Lucas, and Hart do not teach or suggest every element of independent claims 29 and 61, nor would it have been obvious to one of ordinary skill in the art to modify the cited art to produce claims 29 and 61.

The critical deficiencies of Baur are discussed above. Lucas and Hart do not cure the deficiencies of Baur. Rather, Lucas is cited solely as teaching filtering cell suspensions, and Hart is cited solely as teaching that trypsinized skin suspensions contain Langerhans cells. See Office

Action at page 5. Thus, the combination of the references still fails to teach, suggest, or make obvious claims 29 and 61, as well as the claims that depend therefrom.

For the reasons provided above, Applicant respectfully submits that the instant claims are not rendered obvious in view of Baur, Lucas and Hart. Accordingly, Applicants request that the rejection of claims 29, 61, 63, 65 and 75-79 under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the claims, as amended, are in condition for allowance and request early favorable action. If the Examiner believes a telephonic interview would expedite the prosecution of the present application, the Examiner is welcome to contact Applicants' Attorney at the number below.

Respectfully submitted,

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